MEDICAL STAFF CONFERENCE

Medical Management of Chronic Renal Disease

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. SLEISENGER:* Dr. Robert Schrier† will discuss the important clinical topic of medical management of chronic renal failure.

DR. SCHRIER:† The advent of renal transplantation and chronic dialysis has revolutionized the treatment of end-stage renal disease. Nevertheless, medical management remains the primary treatment of most patients with chronic renal failure. Furthermore, patients treated with chronic dialysis or renal transplantation still require a substantial degree of medical management.

Reversible Factors in Chronic Renal Disease

One of the most important aspects of the medical management of the patient with chronic renal failure is a thorough search for reversible factors which may have worsened the patient's already limited renal function. Chart 1 shows the geometric relationship between renal function, creatinine and blood urea nitrogen concentration (BUN). This chart illustrates that on a normal protein intake urea and creatinine clearances may decrease to a level 50 percent below normal with only a very slight increase in BUN and serum creatinine concentration. However, if the initial urea and creatinine clearances are 25 percent of normal, a slight further decrease in the renal clearance of these substances will greatly increase the BUN and serum creatinine concentration. In this circumstance, the loss of literally a few functioning nephrons may convert a well-compensated patient with chronic renal disease to a severely uremic patient. Conversely, the recognition and

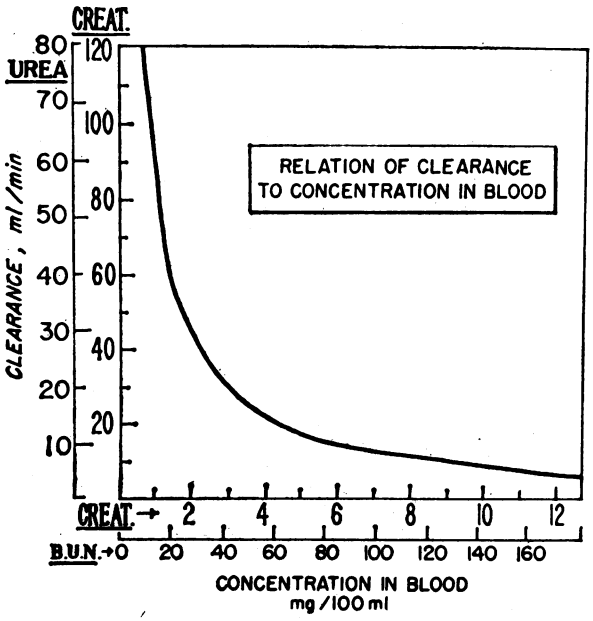

Chart 1.—Rapid rise in blood creatinine concentration and BUN after their renal clearance has diminished to levels greater than 50 percent below normal. Reproduced with permission of publisher.[1]

*Marvin H. Sleisenger, M.D., Professor of Medicine.
†Robert W. Schrier, M.D., Assistant Professor of Medicine.

Table 1.—*Reversible Factors in Chronic Renal Disease*

Urinary Tract Infection	Pericardial Tamponade
Urinary Tract Obstruction	Accelerated Hypertension
Volume Depletion	Electrolyte Disturbances
Congestive Failure	Acute Renal Failure

treatment of reversible factors may produce an equally dramatic improvement in the patient's clinical state in association with a very small increase in glomerular filtration rate (GFR).

The natural history of the renal disease is a primary consideration when searching for reversible factors. For example, in the absence of complicating factors, gradual deterioration of renal function in chronic glomerulonephritis or chronic pyelonephritis occurs over a period of months or years. Deterioration over a period of days or weeks therefore suggests that a potentially reversible factor or factors may have intervened and been responsible for the patient's clinical deterioration. Some of the potentially reversible factors which may worsen the clinical state of a patient with chronic renal disease are shown in Table 1. The detection and treatment of urinary tract infection may arrest or prevent progression of chronic renal failure. Damaged kidneys, whether damaged by congenital abnormalities or disease, seem more prone to infection than structurally normal kidneys; hence, instrumentation or catheterization is best avoided in patients with chronic renal disease. Many urinary tract infections may be asymptomatic or the patient too uremic to allow elucidation of the symptoms; therefore, urine cultures should be a routine procedure in the work-up of patients with chronic renal failure, particularly those with a rapid deteriorating clinical course.

Urinary tract obstruction is a factor to consider in any case of chronic renal disease with rapid clinical deterioration. However, only when conditions strongly suggest it should retrograde pyelography or instrumentation be performed, since, in general, high dose or constant infusion intravenous pyleography is sufficient to exclude obstruction. The most common cause of obstruction is benign prostatic hypertrophy. Suprapubic percussion, postvoid films after intravenous urography, and cystourethrography following suprapubic instillation of contrast material will be sufficient for evaluation of obstruction without instrumentation in patients with chronic renal disease. Since some patients with chronic renal disease may have only one remaining functioning kidney, acute partial or complete obstruction of the remaining kidney may be associated with rapid deterioration. A plain film of the abdomen should always be obtained to exclude the presence of radiopaque calculi. Such a film, with tomography, will also allow evaluation of the kidney size in patients with renal failure. If the kidneys are of normal size, the process causing the renal failure may be acute and thus totally, or at least partially, reversible. However, it should be emphasized that the size may be normal even in end-stage, irreversible renal failure associated with amyloidosis, diabetic glomerulosclerosis and scleroderma, or in rapidly progressive glomerulonephritis.

Depletion of the extracellular fluid volume is probably the most common of the factors which may cause rapid deterioration of renal function. For example, gastroenteritis with nausea, vomiting and diarrhea and an associated decrease in intravascular volume may develop in a patient with compensated chronic renal disease. The decrease in intravascular volume may in turn diminish renal perfusion and GFR and thereby cause a rapid rise in BUN. A vicious cycle may then ensue in which the nausea and vomiting of uremia produce further volume depletion and diminution in renal function. In evaluating a patient with chronic disease a thorough history and physical examination should therefore be obtained in an effort to find out whether volume depletion may be a cause of the decline in clinical state of the patient. The administration of tetracycline may also increase the BUN by inhibiting the rate of anabolism, and the progressive azotemia may in turn initiate a vicious cycle of vomiting, volume depletion and further azotemia.[2] Although a direct nephrotoxic effect of the tetracyclines remains to be established, certain antibiotics, such as kanamycin and colistimethate, may be associated with increased azotemia due to a direct nephrotoxic effect.[3]

Congestive heart failure is another "prerenal" factor which may lead to rapid deterioration of renal disease. Several varieties of congestive heart failure may occur in association with chronic renal disease. However, arteriosclerotic and hypertensive cardiovascular disease and so-called uremic cardiomyopathy are the most common forms. Uremic cardiomyopathy is an ill-defined form of heart disease which has been described in patients with advanced chronic renal failure.[4,5] Severe

cardiac dilatation and arrhythmias are generally present and the associated pulmonary edema may be refractory to digitalis therapy. This form of heart disease has been found to occur particularly in patients with chronic renal disease who are maintained on low-protein diets. Although the cause of heart disease of this type is not known, excessive accumulation of fluid is generally present and its removal is the treatment of choice. In patients with chronic renal disease digitalis preparations should be used with caution in the treatment of congestive heart failure. Since digoxin is excreted primarily by the kidney, it has a prolonged half-life in patients with severe renal impairment.[6] Therefore, in the presence of severe renal impairment the amount of digoxin should be one-half to two-thirds of the normal dose. Rapid changes in potassium concentration during dialysis therapy also predispose patients with chronic renal disease to digitalis toxicity. For these reasons the congestive failure and pulmonary edema associated with severe chronic renal disease is generally best treated by the combination of sodium restriction, diuretics and, when necessary, fluid removal by dialysis rather than the administration of digitalis preparations.

Pericardial tamponade is another important, reversible factor which may occur in patients with chronic renal disease.[7] It should be particularly suspect in patients with chronic renal failure who seem to have predominantly right-sided cardiac failure with increased jugular venous pressure and hepatic congestion. Inspiratory distension of the jugular vein, referred to as Kussmaul's sign, and *pulsus paradoxis* may sometimes be absent. Patients on dialysis who are undergoing heparinization may be particularly prone to hemorrhagic pericardial tamponade. Pericardiocentesis may be life-saving in these circumstances. If pericardiocentesis is not effective in increasing the systemic arterial pressure and decreasing the venous pressure, then the patient should be taken to surgery for open pericardial drainage.

Patients with chronic renal disease frequently have hypertension, and an episode of accelerated hypertension may cause a rapid deterioration in renal function. Moreover, patients with malignant hypertension and encephalopathy may enter the hospital with signs of cerebral depression and neuromuscular irritability which mimic uremia. Control of the hypertension alone, with or without improvement of renal function, may greatly improve the clinical status. Controlling the hypertension may also improve renal perfusion and renal function, although in some instances antihypertensive treatment may be associated with a further deterioration of renal function. The most gratifying improvements in renal function are observed in cases in which accelerated hypertension has precipitated congestive heart failure.

Certain electrolyte disturbances, particularly hypokalemia, may worsen the renal function of patients with chronic renal disease. On the other hand hyponatremia may occur in patients with severe renal impairment and be associated with clinical symptoms which mimic uremia but are actually unrelated to a worsening of renal impairment. It should also be noted that acute renal failure may occur on the background of chronic renal failure. In fact acute renal failure may be more likely to develop in diseased than in normal kidneys.[8] The clinical history may be helpful in suggesting an episode of acute renal failure in patients with underlying chronic renal disease. For example, a history of exposure to nephrotoxic drugs, including antibiotics, or a hypotensive episode might suggest the occurrence of acute renal failure. However, the diagnosis of acute renal failure on the background of chronic renal disease can only be confirmed retrospectively on the basis of the clinical course of recovery.

Abnormalities of Sodium, Water, and Potassium Balance in Chronic Renal Disease

Abnormalities in sodium and water balance are particularly likely to develop in patients with chronic renal disease.[9,10] While most patients with chronic renal disease are able to maintain sodium balance on a normal sodium diet, the institution of a low sodium intake or extrarenal losses of sodium may be associated with volume depletion. On the other hand, these same patients with chronic renal disease may become edematous if placed on a high sodium diet. Thus, patients with advanced chronic renal disease may be poised between edema and volume depletion, and unable to tolerate rapid alterations in sodium balance in either direction. Some patients with chronic renal disease have so-called "salt-losing nephritis" which is featured by an obligatory urinary excretion rate of sodium which exceeds the sodium content of a normal diet. These patients must

therefore ingest large amounts of sodium to maintain sodium balance and avoid volume depletion.[11-13] Cases of "salt-losing nephritis" have most frequently been reported with medullary cystic disease, polycystic disease and pyelonephritis, and they generally occur when the GFR is reduced to less than 10 ml per minute.

Patients with chronic renal disease also have an impaired renal concentration and dilution capacity. Importance of the inability to concentrate urine can be illustrated by the following example. A normal person with a maximal concentrating ability of 1200 milliosmols per liter may excrete a daily solute load of 600 milliosmols in 500 ml of urine per day. In contrast, in advanced chronic renal disease, if the maximum urinary concentrating ability is only 300 milliosmols per liter, then a daily solute load of 600 milliosmols obligates 2 liters of urine per day. Thus, if during a period of extrarenal fluid losses the daily urine output is less than 2 liters, accumulation of solutes, such as urea and creatinine, will occur.

The ability to dilute the urine and excrete a water load is also impaired in patients with chronic renal disease.[14-15] While a normal person may excrete 20 to 30 liters of solute-free water per day without hyponatremia developing, in a patient with advanced chronic renal disease hyponatremia may develop on an oral intake of less than 2 liters per day.

Even with complete suppression of antidiuretic hormone (ADH) and impermeability of the collecting duct the renal capacity to excrete free water is dependent on the volume of fluid delivered to the diluting segment in the distal nephron. In general, this volume approximates 20 percent of the fluid that is filtered at the glomerulus. In a normal person with a GFR of 120 ml per min or 180 liters per day, 36 liters per day would be the approximate volume of fluid delivered to the diluting segment. On the other hand, a patient with severe chronic renal disease and a GFR of 5 ml per min will filter only 7 liters of fluid per day. If 20 percent or 1.4 liters of this filtrate is delivered to the distal diluting segment of the nephron, then this would be the maximal volume of solute-free water which could be excreted per day. Hence, if such a patient is drinking 2 liters or more of water per day, progressive water intoxication and hyponatremia will occur.

"Water-losing nephritis" is a condition which has been described in patients with hypercalcemia or urinary tract obstruction whose urine remains hypotonic to plasma despite the exogenous administration of large doses of vasopressin.[16-18] Such "water-losing nephritis" or "vasopressin-resistant hyposthenuria" also occurs in the majority of patients with severe chronic renal failure.[19] Because of the very low GFR in such patients with advance renal disease, water-losing nephritis is, however, a somewhat inappropriate term. As illustrated earlier, if a patient is filtering only 7 liters of fluid per day, a maximal "water-losing nephritis" may involve the excretion of less than 2 liters of urine per day. The mechanism for the occurrence of vasopressin-resistance hyposthenuria in any of these circumstances is not entirely clear. An increase in solute load per nephron, structural abnormalities in the tubular epithelium which make these structures unresponsive to the action of ADH (endogenous or exogenous) or the interference of the action of ADH by increased calcium excretion per nephron or some "uremic toxin" have all been entertained as possible mechanisms.[19]

The development of hyperkalemia in chronic renal disease is very rare, unless the patient becomes severely oliguric, receives an acute potassium load or is treated with diuretics, such as spironolactone or triamterine.[20] The ability of patients with chronic renal disease to maintain potassium balance is probably the result of two factors: (1) enhanced potassium secretory capacity of the distal tubule and (2) increased fecal losses of potassium. Evidence for the secretion of potassium is frequently present in patients with chronic renal disease since the amount of potassium excreted in the urine may exceed the amount of potassium filtered at the glomerulus. Hyperaldosteronism in chronic renal disease has been suggested to be the mechanism whereby patients with chronic renal disease are able to increase their distal potassium secretion per nephron and maintain a potassium balance.[20-21] The evidence for a state of "hyperaldosteronism" in chronic renal failure has been based on measurements of aldosterone secretory rates.[22,23] Since this method assumes the excretion within 24 hours of the radioisotopic-labeled conjugate of aldosterone, the delayed excretion of the injected isotope which occurs with impaired renal function[22] makes the results difficult to interpret.

Furthermore, the 24-hour urinary excretion rate of aldosterone in chronic renal disease has been recently found to be within the normal range in patients maintained on a normal sodium diet, and to increase only during prolonged sodium restriction.[24] However, plasma aldosterone levels have not been measured in chronic renal disease. Another factor which allows patients with chronic renal disease to maintain potassium balance is the excessive fecal loss of potassium.[24-26] Patients with severe chronic renal disease may lose as much as 50 percent of their oral intake of potassium in their stool, in contrast to negligible losses (less than 10 percent) in normal persons.

Hypokalemia may occur in chronic renal disease and is most frequently related to the administration of diuretics which increase potassium excretion, such as thiazides, furosemide and ethacrynic acid. Potassium-losing nephritis, like sodium-losing nephritis, is a rare occurrence in chronic renal disease.[27] If the decreased reabsorption of sodium in cases of sodium-losing nephritis occurs in the proximal tubule, then the increased delivery of sodium to the site of potassium secretion in the distal nephron may facilitate the secretion of potassium. Renal tubular acidosis, either the classical type or the variety related to a proximal tubular defect in bicarbonate reabsorption in Fanconi's disease is another cause of potassium wasting in chronic renal disease. Secondary hyperaldosteronism (malignant hypertension, volume depletion, etc.) may also be associated with renal potassium wastage and hypokalemia in chronic renal disease.

Abnormalities of Acid-Base, Magnesium, Calcium and Phosphorus Metabolism In Chronic Renal Disease

In general the ability to excrete ammonium is limited in patients with chronic renal disease and net acid excretion is less than the estimated endogenous production.[28] Thus, metabolic acidosis is a frequent occurrence in advanced chronic renal failure. Some investigators have suggested that the severity of the metabolic acidosis is in part moderated by the buffering ability of the alkaline bone salts, and that this permits patients with chronic renal disease to compensate for the inability to excrete their daily complement of nonvolatile acid. This buffering activity of bone may also be a factor involved in the pathogenesis of renal osteodystrophy in patients with chronic renal disease, which will be discussed later. In general, severe metabolic acidosis necessitating treatment does not occur in steady-state conditions in chronic renal disease. However, as with sodium and water metabolism, the ability to respond to additional stressful circumstances is greatly limited. For example, loss of alkali with diarrhea or increased catabolism, as may occur with fever and infection, may be associated with a rapid appearance of severe acidosis. In these circumstances the metabolic acidosis associated with chronic renal failure must be treated with sodium bicarbonate. The danger of such treatment is obviously related to the increased intake of sodium and the potential precipation of volume overload and pulmonary edema. The treatment of the acidosis must therefore be carefully monitored with respect to its effect on the cardiovascular system.

Table 2.—*Disturbances of Calcium and Phosphorus Metabolism in Chronic Renal Disease*

Hypocalcemia
Tetany
Hypercalcemia
Metastatic Calcification
Renal Osteodystrophy
1. Osteomalacia
2. Osteitis Fibrosa Cystica
3. Osteosclerosis

Another electrolyte disturbance which may occur in patients with chronic renal disease is hypermagnesemia.[29] Many of the antacids contain magnesium and therefore should not be prescribed in patients with severe impairment of renal function. The symptoms of acute magnesium intoxication include depression of neuromuscular reflexes, hypotension, depression of respirations and ultimately cardiac arrest.

Disturbances in calcium and phosphorus metabolism are frequent concomitants of chronic renal disease (Table 2). Hypocalcemia is generally present in association with hyperphosphatemia. Correction of the elevation of the serum phosphate in chronic renal disease will not, however, uniformly increase the serum calcium concentration to normal levels. The reason for this persistent hypocalcemia is not clear, and it is of particular interest since it occurs in the face of elevated serum levels of parathormone.[30] Whether this hypocalcemia is in any way related

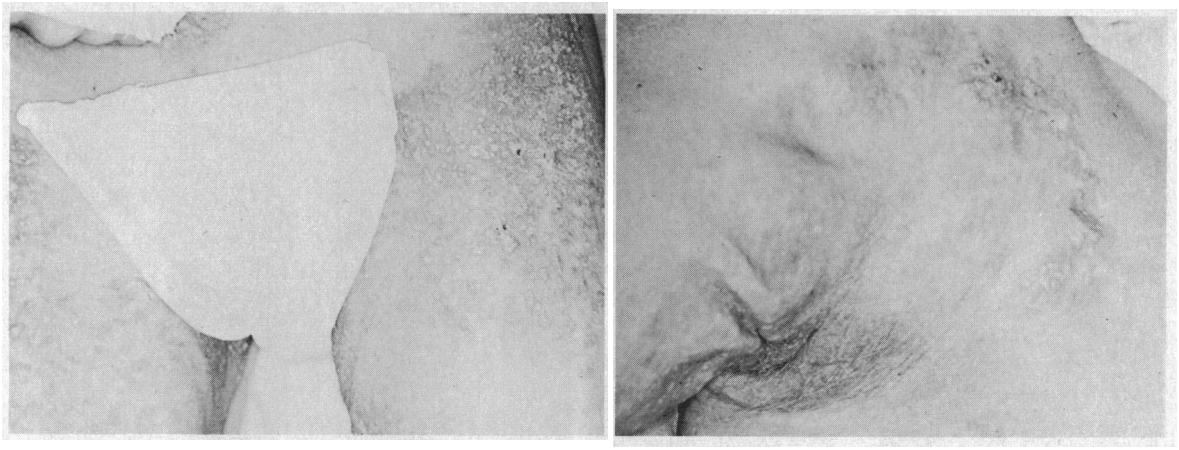

Figure 1.—Metastatic calcification in the thigh (left) and axillary (right) region of patient with advanced chronic renal failure.

to excessive levels of thyrocalcitonin in chronic disease remains to be determined. The hypocalcemia of chronic renal disease is rarely associated with tetany and in general need not be treated. This absence of tetany despite significant hypocalcemia is probably due to the fact that the filtrable or ionized portion of the serum calcium is generally normal in patients with chronic renal disease. Tetany, however, may occur in patients with chronic renal disease if the metabolic acidosis is vigorously treated by the administration of sodium bicarbonate. This rapid change in pH may decrease the portion of calcium which is ionized, and precipitate tetany. We have also recently seen a patient in whom symptoms of tetany secondary to pronounced hyperphosphatemia developed following the administration of phospate-containing enemas in the absence of a decrease in serum calcium concentration.

Hypercalcemia may occasionally occur in patients with chronic renal disease. In general this hypercalcemia is associated with systemic diseases including multiple myeloma, sarcoidosis, metastatic bone lesions, milk-alkali syndrome or vitamin D intoxication. An unusual cause of hypercalcemia recently has been described in the English literature.[31] To avoid the potential danger of a positive sodium balance, calcium (rather than sodium) exchange resins have been used to treat hyperkalemia, and their use has occasionally caused severe hypercalcemia.[31] Autonomous or tertiary hyperparathyroidism may also occasionally be associated with hypercalcemia in chronic renal disease; however, more frequently primary hyperparathyroidism and hypercalcemia have caused the chronic renal disease. After the occurrence of advanced chronic renal disease it may be difficult clinically to distinguish between these two sequences of events.

Metastatic calcification is another very severe complication of calcium-phosphorus metabolism in chronic renal disease. Metastatic calcification may occur in the kidney, in subcutaneous tissues, in blood vessels and even in the myocardium. This metastatic calcification may be associated with pronounced necrosis of the skin and muscle[32] as well as with gangrene of the distal extremities in some instances.[33] Severe metastatic calcifications in the thigh and axillary regions of a patient with advanced chronic renal failure is illustrated in Figure 1. The incidence of the metastatic calcification seems to be in general related to the degree of elevation of the calcium-phosphorus product. The calcium-phosphorus product in patients with chronic renal disease therefore should not be allowed to exceed 60 milligrams per 100 ml. The best means of lowering this product is to lower the serum phosphate level by the administration of nonmagnesium containing phosphate binding antacids which will increase the fecal losses of phosphate.

Renal osteodystrophy is a very frequent complication of advanced chronic renal disease when diagnosed on histological grounds by bone biopsy.[34-35] On the other hand, radiological evidence of renal osteodystrophy is less frequent and symptomatic renal osteodystrophy even more infrequent. However, a small proportion of patients with advanced chronic renal failure will have severe bone pain and evidence of pathological fractures. In general there are three varieties of bone disease which may occur in

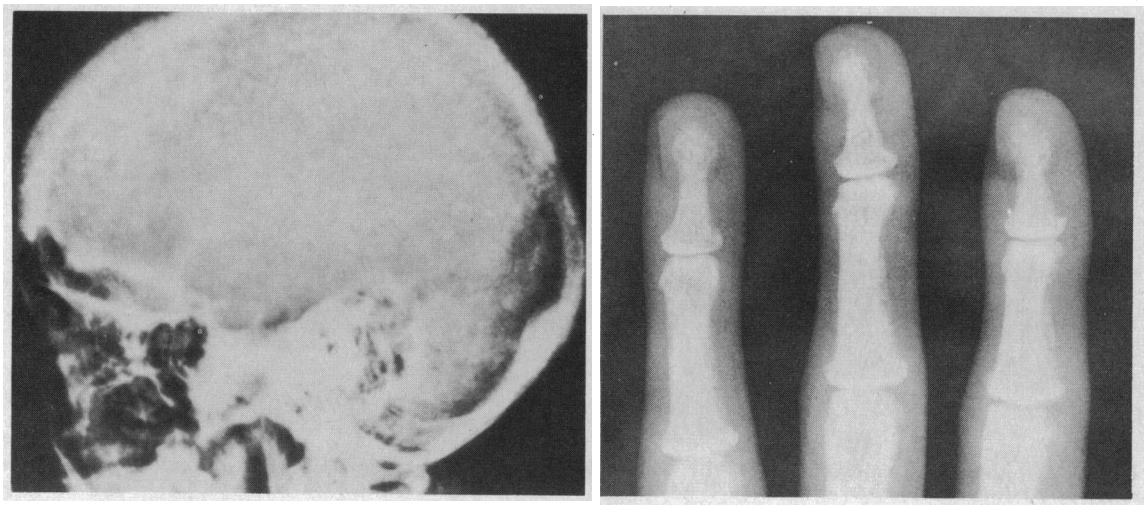

Figure 2.—Renal osteodystrophy: "salt and pepper" pattern in the skull (left) and subperiostial resorption in distal phalanges in patient with advanced renal failure and secondary hyperparathyroidism (right).

chronic renal disease, namely, osteomalacia, osteitis fibrosa cystica (which is indistinguishable from the bone disease that occurs with primary hyperparathyroidism) and osteosclerosis. All three types of bone disease may, and generally do, occur in the same patient. The presence of severe osteitis fibrosa cystica in a patient with chronic renal failure is illustrated in Figure 2. Both the "salt and pepper" appearance in the skull and the subperiostial reabsorption in the distal phalanges are characteristic of this form of renal osteodystrophy. It has been postulated that renal osteodystrophy is caused by resistance to vitamin D. Although normal blood levels of vitamin D have been found in patients with chronic renal disease, [36] a defect in calcium absorption from the gastrointestinal tract has been shown to occur in most of these patients.[37] In normal persons approximately 80 percent of the calcium in the diet appears in the stool; however, in patients with chronic renal disease nearly 100 percent of the oral intake of calcium may be recovered from the stool. Although patients with chronic renal disease excrete very little calcium in the urine,[19,38] the total urine and fecal calcium losses may exceed the oral intake of calcium. This small, daily negative calcium balance over a long period may be an important factor in the pathogenesis of renal osteodystrophy.

Administration of large doses of vitamin D has been shown to increase the gastrointestinal absorption of calcium in chronic renal disease, and this positive calcium balance is associated with improvement in the bone disease. The danger of the administration of vitamin D in chronic renal disease is that prolonged hypercalcemia and metastatic calcification may occur. This complication may be difficult to treat because the half-life of vitamin D may be several weeks in patients with chronic renal failure. The occurrence of hypercalcemia with vitamin D therapy is most frequently seen in patients with chronic renal disease who have a normal serum calcium concentration before vitamin D therapy, and thus perhaps the most pronounced secondary hyperparathyroidism.[39] In some of these patients parathyroidectomy may be necessary before treatment with vitamin D is begun.

While it is quite clear that large doses of vitamin D may improve the bone disease in patients with chronic renal disease, this does not necessarily implicate "vitamin D resistance" as the main pathogenetic factor in the osteodystrophy. In fact a recent study suggests that the defect in calcium transport in the intestine during uremia is independent of either intestinal calcium binding protein or vitamin D activity.[40] Moreover, de Wardener and associates[41] have been able to improve the bone disease in chronic renal disease by the oral administration of calcium carbonate or calcium phosphate salts. In these studies a positive calcium balance occurred in the absence of vitamin D administration. Since the administration of vitamin D, calcium salts or parathyroidectomy may be associated with complications, only patients with symptoms of renal osteodystrophy or severe radiological evidence of renal osteodystrophy should be treated. In

children the decision concerning treatment is more acute because the renal osteodystrophy may be associated with stunting of growth and abnormalities of gait.

Neuromuscular Disturbances in Chronic Renal Disease

The neuromuscular disturbances which occur in patients with advanced chronic renal failure are the hallmark of clinical uremia. Occurrence of neuromuscular symptoms provides the best evidence that the medical management has been inadequate, and either reversible factors must be found and treated or more definitive therapy, such as chronic dialysis or renal transplantation, be instituted. Some of the neuromuscular disturbances associated with uremia are somewhat subtle, such as increased emotional lability, insomnia or inability to concentrate, while other symptoms, such as asterixis, coma and convulsions are more dramatic. If the more subtle symptoms can be detected, treatment can be started in time to avert the life-endangering symptoms of coma and convulsions. Although a specific "uremic toxin" which causes the central nervous system manifestations of uremia has not been identified, in experiments with dogs these symptoms have been simulated by the chronic administration of quanidinosuccinic acid.[42]

Both sensory and motor peripheral neuropathy may develop in patients with chronic renal disease.[43] One of the first findings is the "restless leg syndrome"[44] or paresthesias in the distal extremities.[43] The motor involvement generally occurs later and may progress to either para-or quadraplegia. In most instances dialysis will either arrest or even improve the sensory peripheral neuropathy but motor neuropathy may be irreversible.[45] The pathogenesis of the neuropathy seems to be unrelated to either diabetes mellitus or vitamin deciency and the responsible mechanisms remain to be explained. Histologically, the damage in the peripheral nerve occurs in the distal portion of the medullated fibers and involves a loss of myelin. This histological finding has raised the possibility that there is a decrease in delivery of some necessary component of metabolism to the distal part of the nerve fiber but this hypothesis remains to be proved.

Significant delay in the nerve conduction time may be used as a criteria for the institution of more definitive management, that is, renal transplantation or chronic dialysis.[45,46] Some other neuromuscular disturbances which occur in chronic renal failure are acute blindness, nystagmus, miosis and pupil asymmetry.[43]

Table 3.—*Hematological Disturbances in Chronic Renal Disease*

I.	Anemia
	A. Hemolytic Component
	1. Extracorpuscular Factor
	B. Decreased Erythropoiesis
	1. Low Erythropoietin Levels
	2. Suppressive Effect of Transfusions
	C. Iron Deficiency
	D. Folic Acid Deficiency
II.	Hemorrhagic Tendency
	A. Gastrointestinal Irritation with Ammonia
	B. Platelet Defect
	1. Inhibition or Destruction of Platelet Factor 3

Table 4.—*Carbohydrate and Lipid Disturbances in Chronic Renal Disease*

I.	Carbohydrate Intolerance in Uremia
	A. Normal Fasting Blood Sugar
	B. Abnormal Glucose Tolerance Test
	1. Insulin-resistance Secondary to Peripheral Antagonism
II.	Hypertriglyceridemia
	A. Increased Hepatic Synthesis of Triglyceride-rich Lipoprotein
	B. Decreased Post-heparin Lipolytic Activity

Hematological Disorders in Chronic Renal Disease

Hematological disorders (Table 3) are a very frequent occurrence in chronic renal disease, and anemia in particular occurs in almost every case. In fact, if a patient enters the hospital with severe renal impairment and a normal hematocrit, an acute cause of the renal failure should be considered. In general, transfusions should not be used to treat the anemia, since the administration of multiple transfusions is associated with numerous complications including transfusion reactions, hemosiderosis, viral hepatitis and suppression of erythropoiesis. In the absence of multiple transfusions, the hematocrit in patients with advanced renal failure will generally stabilize in the range of 20 to 25 values percent, a level which is well tolerated unless the patient has severe arteriosclerotic cardiovascular disease.

The anemia seems to be etiologically related to two factors, namely, hemolysis and suppression of erythropoiesis.[47,48] Chart 2 shows the correlation between the shortened half-life of chromium-tagged red blood cells and the degree

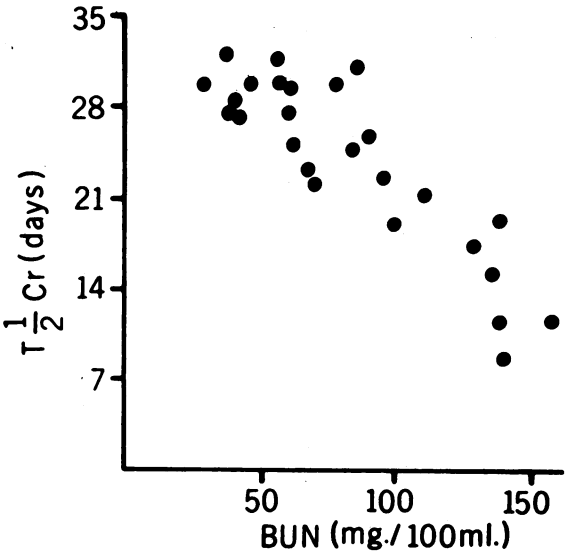

Chart 2.—Relationship between shortened half-life of chronium-labeled red blood cells and BUN in chronic renal failure. Reproduced with permission of publisher.[49]

of the azotemia.[49] The cause of this hemolysis seems to be related to an extracorpuscular factor. Red blood cells from uremic patients have a normal half-life when transfused into normal subjects. Conversely, red blood cells from normal subjects have a shortened half-life when transfused into uremic patients. The degree of hemolysis is, however, relatively mild and with a normally functioning bone marrow would not lead to any significant degree of anemia. Thus the suppression of erythropoiesis seems to be the most significant factor in the anemia of chronic renal disease. Bioassays of erythropoietin have indicated that patients with chronic renal disease have considerably lower blood levels of erythropoietin than normal subjects. Thus, decreased erythropoietin levels have been suggested as a cause of the suppression of erythropoiesis in chronic renal failure. However, measurable increases in erythropoietin levels have not been uniformly found in dialysis patients who have demonstrated an increase in erythropoiesis and hematocrit after control of uremia with dialysis and withholding transfusions for six months to two years.[50] Therefore, while the suppression of erythropoiesis may be related in part to a decrease in erythropoietin production, additional factors may be involved.

An additional cause of anemia in chronic renal disease is iron deficiency which may be due to blood loss from the gastrointestinal tract or into the dialysis machine. Folic acid deficiency has also been described as a cause of anemia in patients with chronic renal disease on maintenance dialysis.[51] Another hematological disorder which is well known to occur in patients with advanced renal failure is an increased hemorrhagic tendency. Gastrointestinal hemorrhage may be related to the direct chemical irritation of urea on the mucosa; however, the overall hematological tendency of renal failure has been related to an inhibition of destruction of platelet factor 3.[52]

Disorders of Glucose and Lipid Metabolism in Chronic Renal Disease

Approximately 70 percent of patients with uremia have an abnormal glucose tolerance test. This "uremic diabetes" does not seem to be related to an inability of the pancreas to secrete insulin, since the initial response of plasma insulin levels to intravenous glucose is decreased in diabetic patients and is normal in patients with uremia. This finding has led most investigators to feel that "uremic diabetes" is due to an antagonism of the peripheral action of insulin. *In vitro* dialysis of uremic serum has failed to abolish this insulin-resistance, as assayed on rat diaphragm.[53] However, chronic dialysis in patients is known to normalize the glucose tolerance test in uremic patients.[54] These findings suggest that the antagonism to the action of insulin in uremic patients is at the level of the peripheral tissues rather than antagonism by a circulating substance. The clinical importance of the glucose intolerance in patients with uremia is related to the problems of selecting patients for chronic dialysis and renal transplantation. Patients with diabetes mellitus are in general less suitable candidates for this more definitive treatment because of their high incidence of progressive vascular complications. The measurement of the fasting blood sugar is an easier means than measuring plasma insulin levels to differentiate true diabetes mellitus from "uremic diabetes." While the fasting blood sugar is abnormal in patients with diabetes mellitus, it is generally normal in patients who demonstrate the glucose intolerance of uremia. (See Table 4.)

Hypertriglyceridemia is another metabolic abnormality which occurs in association with chronic renal disease.[55] The cause of this hypertriglyceridemia seems to be related to both an increase in hepatic synthesis of triglyceride-rich

lipoprotein and the decreased clearing activity of lipoprotein lipase. The clinical significance of this hypertriglyceridemia remains to be established.

In summary, the medical management of patients with chronic renal disease is a very important aspect of their care. The clinician must search for and treat reversible factors which may improve or prevent further deterioration of renal function. If such reversible factors are not found and treated, advanced renal failure may be associated with abnormalities in virtually every organ system and make the medical management very difficult even for the most astute of clinicians. As Homer Smith[56] put it in his book *From Fish to Philosopher:*

> Bones can break, muscles can atrophy, glands can loaf, even the brain can go to sleep, without immediately endangering our survival; but should the kidneys fail . . . neither bone, muscle, gland, nor brain could carry on.

REFERENCES

1. Strauss MB, Welt LG: Diseases of the Kidney. Boston, Little, Brown and Co, 1963, p 101

2. Shils ME: Renal disease and the metabolic effects of tetracycline. Ann Intern Med 58:389-408, 1963

3. Kunin CM: A table of recommended doses and factors governing serum levels. Ann Intern Med 67:151-158, 1967

4. del Greco F, Shere J, Simon NM: Hemodynamic effects of hemodialysis in chronic renal failure. Trans Amer Soc Artif Intern Organs 10:353-355, 1964

5. Bailey GL, Hampers C, Merrill JP: Reversible cardiomyopathy in uremia. Trans Amer Soc Artif Intern Organs 13:263-270, 1967

6. Doherty JE, Flanigan WJ: Studies with tritiated digoxin in anephric human subjects. Circulation 35:298-302, 1967

7. Bailey GL, Hampers CL, Hager EB, et al: Uremic pericarditis. Circulation 38:582-591, 1968

8. Schrier RW, Bulger RJ, Van Arsdel PP: Nephropathy associated with penicillin and homologues. Ann Intern Med 64:116-127, 1966

9. Platt R: Structural and functional adaptation in renal failure. Brit Med J 1:1313-1317 and 1372-1377, 1952

10. Bricker NS: On the meaning of the intact nephron hypothesis. Amer J Med 46:1-11, 1969

11. Thorn GW, Koepf GF, Clinton Jr M: Renal failure simulating adrenocortical insufficiency. New Eng J Med 231:76-85, 1944

12. Stanbury SW, Mahler RF: Salt-wasting renal disease—Metabolic observations on a patient with "salt-losing nephritis." Quart J Med 28:425-447, 1959

13. Walker WF, Jost L, Johnson Jr, et al: Metabolic observations on salt wasting in a patient with renal disease. Amer J Med 39:505-519, 1965

14. Kleeman CR, Adams DA, Maxwell MH: An evaluation of maximal water diuresis in chronic renal disease—I. Normal solute intake. J Lab Clin Med 58:169-184, 1961

15. Adams DA, Kleeman CR, Bernstein LH, et al: An evaluation of maximal water diuresis in chronic renal disease—II. Effect of variations in sodium intake and excretion. J Lab Clin Med 58:185-196, 1961

16. Roussak NJ, Oleesky S: Water-losing nephritis; Syndrome simulating diabetes insipidus. Quart J Med 23:147-164, 1954

17. Berlyne GM: Distal tubular function in chronic hydronephrosis. Quart J Med 30:339-355, 1961

18. Carone FA, Epstein FH: Nephrogenic diabetes insipidus caused by amyloid disease: Evidence in man of role of collecting ducts in concentrating urine. Amer J Med 29:539-544, 1960

19. Tannen RL, Regal EM, Dunn MJ, et al: Vasopressin-resistant hyposthenuria in advanced chronic renal disease. New Eng J Med 280:1135-1141, 1969

20. Kleeman CR, Okun R, Heller RJ: The renal regulation of sodium and potassium in patients with chronic renal failure (CRF) and the effect of diuretics on the excretion of these ions. Ann NY Acad Sci 139:520-539, 1966

21. Gerstein AR, Kleeman CR, Gold EM, et al: Aldosterone deficiency in chronic renal failure. Nephron 5:90-105, 1968

22. Cope CL, Pearson J: Aldosterone secretion in severe renal failure. Clin Sci 25:331-341 1963

23. Gold EM, Kleeman CR, Ling S, et al: Sustained aldosterone secretion in chronic renal failure. Clin Res 13:135, 1965

24. Schrier RW, Regal EM: Role of aldosterone in sodium, water and potassium metabolism during sodium restriction in chronic renal disease (Submitted for Publication)

25. Hayes CP Jr, Robinson RR: Fecal potassium excretion in patients on chronic intermittent hemodialysis. Trans Amer Soc Artif Int Organs 11:242-246, 1965

26. Hayes CP Jr, McLeod ME, Robinson RR: An extrarenal mechanism for the maintenance of potassium balance in severe chronic renal failure. Trans Assoc Amer Physic 80:207-216, 1967

27. Sebastian A: Medical Staff Conference: The clinical spectrum of renal potassium wasting. Calif Med 110:493-500, 1969

28. Relman AS: The acidosis of renal disease. Amer J Med 44: 706-713, 1968

29. Randall RE, Jr, Cohen MD, Spray CC, et al: Hypermagnesemia in renal failure—Etiology and toxic manifestations. Ann Intern Med 61:73-88, 1964

30. Berson SA, Yalow RS: Parathyroid hormone in plasma in adenomatous hyperparathyroidism, uremia, and bronchogenic carcinoma. Science 154:907-909, 1966

31. Papadimitriou M, Gingell JC, Chisholm GD: Hypercalcemia from calcium ion-exchange resin in patients on regular hemodialysis. Lancet 2:948-950, 1968

32. Richardson JA, Herron G, Reitz R, et al: Ischemic Ulcerations of skin and necrosis of muscle in azotemic hyperparathyroidism. Ann Intern Med 71:129-138, 1969

33. Friedman SA, Novack S, Thomson GE: Arterial calcification and gangrene in uremia. New Eng J Med 280:1392-1394, 1969

34. Dent CE, Harper CM, Phipot GR: The treatment of renal-glomerular osteodystrophy. Quart J Med 30:1-31, 1961

35. Stanbury SW, Lumb GA. Parathyroid biochemistry in azotemic renal osteodystrophy. Quart J Med 35:1-23, 1966

36. Avioli LV, Slatopolsky E: The absorption and metabolism of vitamin D in chronic renal failure. J Clin Invest 46:1032-1033, 1967

37. Ogg CS: The intestinal absorption of Ca by patients in chronic renal failure. Clin Sci 34:467-471, 1968

38. Better OS, Kleeman CR, Gonick HC, et al: Renal handling of calcium, magnesium and inorganic phosphate in chronic renal failure. Israel J Med Sci 3:61-79, 1967

39. Stanbury SW: Treatment of renal osteodystrophy (Editorial). Ann Intern Med 65:1133-1138, 1966

40. Baerg RD, Kimberg DV, Gershon E: Effect of renal insufficiency on the active transport of calcium by the small intestine. J Clin Invest 49:1288-1300, 1970

41. Curtis JR, Wing AJ, Eastwood JB, et al: The control of metabolic bone disease by maintenance hemodialysis. Proc Fifth European Dialysis and Transplantation Association, Dublin 1968

42. Giovannetti S, Biaglni M, Balestri PL, et al: Uremic symptoms in dogs chronically intoxicated with methylguanidine. Presented at the Fourth International Congress of Nephrology, Stockholm, June 22-27, 1969 p 43

43. Tyler HR: Neurologic disorders in renal failure. Amer J Med 44:734-748, 1968

44. Callaghan N: Restless legs syndrome in uremic neuropathy. Neurology (Minneap) 16:359-361, 1966

45. Tenckhoff HA, Boen FST, Jebsen RH, et al: Polyneuropathy in chronic renal insufficiency. JAMA 13:91-94, 1965

46. Blagg CR, Kemble F, Taverner D: Nerve conduction velocity in relationship to the severity of renal disease. Nephron 5:290-299, 1968

47. Eschbach JW Jr, Funk D, Adamson J, et al: Erythropoiesis in patients with renal failure undergoing chronic dialysis. New Eng J Med 276:653-658, 1967

48. Nathan DG, Beck LH, Hampers CL, et al: Erythrocyte production and metabolism in anephric and uremia men. Ann NY Acad Sci 149:539-543, 1968

49. Adamson JW, Eschbach J, Finch CA: The kidney and erythropoiesis Amer J Med 44:725-733, 1968

50. Eschbach Jr: Anemia and hemodialysis. Proc Fourth International Congress of Nephrology, Stockholm, Sweden, 1969, p 161

51. Hampers CL, Streiff R, Nathan DG, et al: Megaloblastic hematopoiesis in chronic renal failure. Clin Res 14:379, 1966

52. von Kaulla KN, von Kaulla E, Wasantapruck S, et al: Blood coagulation in uremia patients before and after hemodialysis and transplantation of the kidney. Arch Surg (Chicago) 92:184-191, 1966

53. Davidson MB, Lowrie EG, Hampers CL: Lack of dialyzable insulin antagonist in uremia. Metabolism 18:387-394, 1969

54. Hampers CL, Soeldner JS, Doak PB, et al: Effect of chronic renal failure and hemodialysis on carbohydrate metabolism. J Clin Invest 45:1719-1731, 1966

55. Bagdade JD, Porte D Jr, Bierman EL: Hypertriglyceridemia: A metabolic consequence of chronic renal failure. New Eng J Med 279: 181-185, 1968

56. Smith, HW: From Fish to Philosopher: The Story of Our Internal Environment. Summit, NJ, Ciba Phar Co Inc, 1959